A Novel Role for an RNA Polymerase III Subunit POLR3G in Regulating Pluripotency in Human Embryonic Stem Cells.

Journal: Stem Cells

Publication Year: 2011

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PubMed link: 21898682

Funding Grants: Improved hES Cell Growth and Differentiation, The University of California: Irvine Regional Human Embryonic Stem Cell Shared Research Laboratory and Stem Cell Techniques Course, UCI-CIRM Research Training Program II, Stem Cell Research Training Grant

Public Summary:
The pluripotency of human embryonic stem cells (hESC) could have great potential for the development of cell replacement therapies. Previous studies have converged on the finding that the OCT4, SOX2 and NANOG genes serve as key regulators in the maintenance of hESC. However, other signals that regulate hESC maintenance remain poorly studied. Here we describe a novel role of an RNA polymerase III (Pol III) subunit, POLR3G, in the maintenance of pluripotency in hESC. We demonstrate the presence of POLR3G in undifferentiated hESC, human induced pluripotent stem cells (hiPSC) and early mouse blastocysts. Downregulation of POLR3G is observed upon differentiation of hESC and hiPSC, suggesting POLR3G can be used as a molecular marker to readily identify undifferentiated pluripotent stem cells from their differentiated derivatives. Using an inducible shRNA lentiviral system, we found evidence that decreased levels of POLR3G result in loss of pluripotency and promote differentiation of hESC to all three germ layers, but have no effect on cell apoptosis. On the other hand, overexpression of POLR3G has no effect on pluripotency and apoptosis in undifferentiated hESC. Interestingly, hESC expressing elevated levels of POLR3G are more resistant to differentiation. Furthermore, our experimental results show that POLR3G is a downstream target of OCT4 and NANOG, and our pharmacological study indicated that POLR3G expression can be readily regulated by the Erk1/2 signaling pathway. This study is the first to show an important role of POLR3G in the maintenance of hESC, suggesting a potential role of Pol III transcription in regulating hESC pluripotency. These studies could have important implications for understanding how to grow human ES cells and how to make pluripotent stem cells from specialized cells.

Scientific Abstract:
The pluripotency of human embryonic stem cells (hESC) could have great potential for the development of cell replacement therapies. Previous studies have converged on the finding that OCT4, SOX2 and NANOG serve as key regulators in the maintenance of hESC. However, other signals that regulate hESC maintenance remain poorly studied. Here we describe a novel role of an RNA polymerase III (Pol III) subunit, POLR3G, in the maintenance of pluripotency in hESC. We demonstrate the presence of POLR3G in undifferentiated hESC, human induced pluripotent stem cells (hiPSC) and early mouse blastocysts. Downregulation of POLR3G is observed upon differentiation of hESC and hiPSC, suggesting POLR3G can be used as a molecular marker to readily identify undifferentiated pluripotent stem cells from their differentiated derivatives. Using an inducible shRNA lentiviral system, we found evidence that decreased levels of POLR3G result in loss of pluripotency and promote differentiation of hESC to all three germ layers, but have no effect on cell apoptosis. On the other hand, overexpression of POLR3G has no effect on pluripotency and apoptosis in undifferentiated hESC. Interestingly, hESC expressing elevated levels of POLR3G are more resistant to differentiation. Furthermore, our experimental results show that POLR3G is a downstream target of OCT4 and NANOG, and our pharmacological study indicated that POLR3G expression can be readily regulated by the Erk1/2 signaling pathway. This study is the first to show an important role of POLR3G in the maintenance of hESC, suggesting a potential role of Pol III transcription in regulating hESC pluripotency.